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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/693,164

10/24/2003

Carson R. Loomis

NRK.092

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10/05/2006

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EXAMINER

LANDSMAN, ROBERT S

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/693,164

Applicant(s)

LOOMIS ET AL.

Examiner

Robert Landsman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 8-27, 55-58, 62-81, 109 and 110 is/are pending in the application.
- 4a) Of the above claim(s) 15 and 69 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 8-14, 16-27, 55-58, 62-68, 70-81, 109 and 110 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/21/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Formal Matters

- A. The Amendment filed 6/9/06 has been entered into the record.
- B. Claims 1-4, 8-27, 55-58, 62-81, 109 and 110 are pending. Claims 15 and 69 are withdrawn as being drawn to a non-elected invention. Therefore, claims 1-4, 8-14, 16-27, 55-58, 62-28, 70-81, 109 and 110 are the subject of this Office Action.
- C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Objections

- A. All objections to the claims have been withdrawn in view of Applicants' cancellation of, or amendments to the claims. However, new claim objections appear below.
- B. Claims 3 and 57 are objected to since the syntax can be improved by reciting "arrestin or to the TMR."
- C. At least claims 21-27 and 75-81 are objected to since the term "dose response" should be hyphenated.
- D. Claims 24 and 78 are objected to since the syntax can be improved by adding the word "the" between "wherein" and "dose."

3. Claim Rejections - 35 USC § 112, first paragraph - enablement

- A. Claims 1-4, 8-14, 16-27, 55-58, 62-68, 70-81, remain rejected and new claims 109 and 110 are also rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 3-7 of the Office Action mailed 2/9/06. Applicants argue that this assay is a general assay for any TMR. This argument has been considered, but is not deemed persuasive. It appears that the specification, as well as the art, is enabling for GPCRs. However, the breadth of the claims is drawn to non-GPCRs. Applicants do not provide any guidance or working examples of TMRs other than that of GPCRs.

Applicants further argue that it would be apparent to one skilled in the art that a biologically active fragment of a TMR can activate intracellular signaling and that biologically active fragments of

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arrestin are also known. These arguments have also been considered, but are not persuasive. While the claims are drawn to methods and not to the molecules themselves, the specification still does not disclose what regions of GPCRs or TMRs are required for biological activity. Again, the breadth of the receptors of the claimed methods is excessive. Furthermore, though Applicants define "biological activity" in the specification, the definition is drawn only to "activating intracellular signaling." However, the breadth of "biological activity" has not been limited to this in the claims, or specification. If Applicants wish to obtain the claimed breadth, the Examiner requests that Applicants provide prior art references showing that a number of "biologically active" GPCRs were known in the art. However, it is suggested that these active GPCRs be focused on identifying those regions which can activate intracellular signaling. Similarly, if Applicants wish to pursue "biologically active" fragments of arrestin, it is suggested that Applicants provide prior art references showing that these fragments were known in the art. Providing these references, however, is not guarantee of a withdrawal of the rejection.

It is believed that all pertinent arguments have been addressed.

4. Claim Rejections - 35 USC § 112, second paragraph – written description

A. Claims 1-4, 8-14, 16-27, 55-58, 62-68, 70-81 remain rejected and new claims 109 and 110 are also rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 7-10 of the Office Action mailed 2/9/06. Applicants argue that numerous arrestins as well as hundreds of GPCRs were known at the time of the invention. However, as discussed above under 35 USC 112, first paragraph – enablement, the claims are not limited to GPCRs, nor have Applicants identified which regions of these GPCRs and arrestins are required to retain their biological activity.

It is believed that all pertinent arguments have been addressed.

5. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, except for claims 1 and 55, regarding "biologically active" have been withdrawn in view of amendments to, or cancellation of, the claims. A discussion of "biologically active," as well as further rejections appear below.

B. Claims 1 and 55, as well as dependent claims 2-5, 8-27, 56-58, 62-81 remain rejected and new claims 109-110 are also rejected under 35 USC 112, second paragraph, for the reasons already of record

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on pages 13-14 of the Office Action mailed 2/9/06. Applicants argue that TMRs “can activate intracellular signaling” and that it would be apparent to the artisan what is a “biologically active” fragment of a TMR or arrestin. These arguments have been considered, but are not deemed persuasive. It is suggested that the claims be amended to recite, for example, “or a fragment thereof which can activate intracellular signaling.” A similar approach should be used regarding “biologically active” arrestin fragments. It is noted that that amendment will not necessarily overcome the rejection of this phrase under 35 USC 112, first paragraph.

C. Claims 1-4, 8-14, 16-27, 55-58, 62-28, 70-81, 109 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 55, part (e), the phrase “and wherein the signaling is activated as compared to...” is unclear. It is believed the claim should read “and wherein the signaling in the presence of the TMR agonist as compared to...”

Furthermore, in claim 55 (e), it is not clear to which signaling the claim refers. There is a test compound, a control compound, or possibly both.

D. Claims 1-4, 8-14, 16-27, 55-58, 62-28, 70-81, 109 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a control in part (f) of claim 1. It is believed that the reduced TMR internalization as compared to the control compound identifies a TMR agonist. The situation is similar for claim 55.

Furthermore, in claims 1 and 55, the goal of the method (preamble) is to identify a TMRA with reduced internalization. However, the conclusion step does not recite this. All that is required is that a TMRA is identified. However, since a TMRA was used in the preamble and previous method steps, no goal has been achieved.

E. Claims 2, 10, 11, 56, 64 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The acronym “GPCR” should be spelled out upon first use.

F. At least claims 3, 9, 12, 13, 21, 22, 24, 26, 27, 57, 63, 66, 67, 75, 76, 78, 80, 81 recite the limitation “the translocation.” There is insufficient antecedent basis for this limitation in the claim.

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G. Claims 9 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the claims should be amended to recite of what the localization is being determined. In other words, “by determining the localization of...in the plasma membrane...”

H. Claims 17, 18, 71 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: those which clarify what these claims are trying to determine.

I. Claims 24, 25, 78 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how to determine that the dose-response curves are “reduced” or “greater” than those of control without measuring Max or EC50. The terms “reduced” and “greater” are arbitrary.

J. Claims 55-58, 62-81 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In parts (c) and (d) of claim 55, it is unclear to which “compound” the claim refers. There are “control” and “test” compounds.

6. Claim Rejections - 35 USC § 102

A. Claims 1-3, 5, 9, 11-13, 16, 20, 55-59, 63-67, 70 and 74 remain rejected under 35 USC 102 as being anticipated by Barak et al. (U.S. Patent 6,110,693) for the reasons already of record on pages 12-15 of the Office Action mailed 2/6/06. Applicants argue that Barak do not teach measuring the translocation of a TMR in the presence of a test and control compound. This argument has been considered, but is not deemed persuasive. While Barak do not specifically teach the direct measurement of TMR, the patent does disclose comparing the translocation of labeled arrestin, not of the TMR itself (column 12, lines 14-43). Though Applicants may argue this does not meet the limitations of the present claims, it is brought to Applicants' attention that the claims, e.g. claim 3, recite measuring TMR by monitoring a detectable molecule bound to arrestin. Therefore, it does not appear that measuring the actual TMR is required by the present claims and that an indirect measurement can be achieved by measuring arrestin, which is disclosed by Barak (column 12, lines 14-43). The process steps of the invention and art are the same regardless of whether the TMR or arrestin is being measured (Ex parte Novitski, 26 USPQ 1391). The

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instant process claims would inherently possess TMR internalization as implied by at least claim 3 of the present invention.

7. Claim Rejections - 35 USC § 103

A. Claims 1, 4, 10, 19, 58, 64 and 73, remain rejected under 35 USC 103 as being unpatentable over Barak in view of Knudsen for the reasons already of record on pages 15-18 of the Office Action mailed 2/9/06. **Claims 2, 3, 8, 9, 11-14, 16-18, 20-27, 55-57, 62, 63, 65-68, 70-72 and 74-81 are also being added to this rejection as well as new claim 109 and 110.** Therefore, claims 1-4, 8-14, 16-27, 55-58, 62-68, 70-81, 109 and 110 are rejected.

Applicants argue that Barak fail to meet all the limitations of the claimed invention, as discussed above under 35 USC 102 and that Knudsen fail to fill these deficiencies. These arguments have been considered, but are not deemed persuasive. Applicants argue that Barak do not teach measuring the translocation of a TMR in the presence of a test and control compound. While this may be true, Barak do compare the translocation of labeled arrestin, not of the TMR itself (column 12, lines 14-43) in the presence of a test and control compound. Since it is well known that the arrestins bind to an permit internalization of a TMR, it would have been obvious for one of ordinary skill in the art at the time of the present invention to have measured either the translocation of the labeled arrestin, or the affected TMR. It would simply be a matter of labeling the TMR as opposed to the arrestin. One of ordinary skill in the art would have been motivated to measure this TMR in order to more definitively track translocation (i.e. internalization) as compared to arrestin. There would have been a high expectation of success since labeling TMR would have been as basic a method as labeling arrestin since both proteins can be labeled by the same technique.

It also would have been obvious to the artisan to have used this procedure on any TMR, including a GPCR (claim 2, 10, 11). A longer signal activation (claim 8) would be an inherent property of the TMRA and identifying where in the cell the TMR is localized would have also been obvious and easily detectable with a labeled TMR (claim 9, 12). Further optimization of the assay conditions would also have been obvious to better understand the time course (claim 13, 14) and differences among species (claim 18). Measuring dose-response curves and Max response is the most common means to measure/compare ligand effects (claims 22-27).

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8. Conclusion

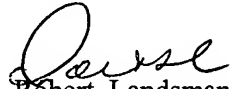
A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on M-Th 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Robert Landsman
Primary Examiner
Art Unit 1647